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A NEW SYNTHETIC STRATEGY FOR HETEROANTHRACYCLINES: TOTAL SYNTHESIS OF D-RING THIOPHENE ANALOGS OF DAUNOMYCIN

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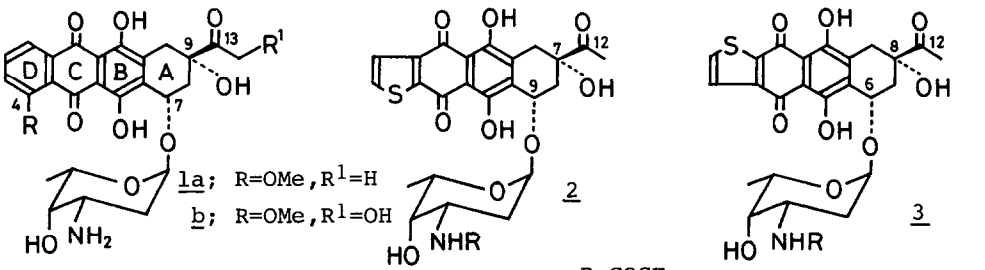
Summary: The strong base-induced cycloaddition of appropriately functionalized thiophene analogs of homophthalic anhydride constitutes a highly regiospecific and convenient route to the D-ring thiophene analogs (2 and 3) of daunomycin.

The anthracycline antibiotics such as daunomycin (1a) and adriamycin (1b) are important antitumor agents in clinical use, but they have severe risk of cardiotoxicity attending their administration.[1] Consequently there is an urgent need to decrease side effects in these valuable agents by appropriate structural modification. Some progress has been made by a modification of the chromophore structure in a series of daunomycin derivatives.[2] From the point of view that the 4-demethoxyanthracyclines are much more potent than the ordinary anthracyclines[1a,3] and heteroaromatic ring can often provide a useful bioisosteric replacement of the benzene ring in some drugs,[4] it is of great interest to synthesize the anthracycline analogs in which D-ring is heterocycle. Although numerous efforts have been made for the preparation of anthracyclines themselves,[5] only a few successful examples have been reported[6,7] to date directed toward the synthesis of heteroanthracyclines involving modifications within the D-ring due to the synthetic obstacle.

We wish to report the first total synthesis of D-ring thiophene analogs (2 and 3)[7] of 1a, which involves a novel and practical process for the regiocontrolled assembly of linearly condensed D-ring heterotetracyclic compounds. Synthetic strategy of 2 and 3, based on a strong base-induced cycloaddition of homophthalic anhydrides recently developed by our group,[8] is shown in Scheme I. Two key features involve the exploitation of 2-acetoxy-2-(2-carboxy-5-trimethylsilylthiophen-3-yl)acetic acid, anhydride (4) as a versatile partner with the chloroquinone acetals in the regiospecific cycloaddition reaction leading to the tetracyclic compounds and the utilization of benzeneboronic acid in the presence of CF_3CO_2H to obtain the cis-diols via the cyclic cis-boronate intermediates.

The unknown anhydride (4) was prepared in excellent yield from (2-carboxythiophen-3-yl)acetic acid (5)[9] through a lead tetraacetate (LTA) oxidation of the tetra-trimethylsilylated ketene acetal intermediate (6). Treatment of 5 with fourfold excess of LDA gave the tetraanion,[10] which was quenched with excess



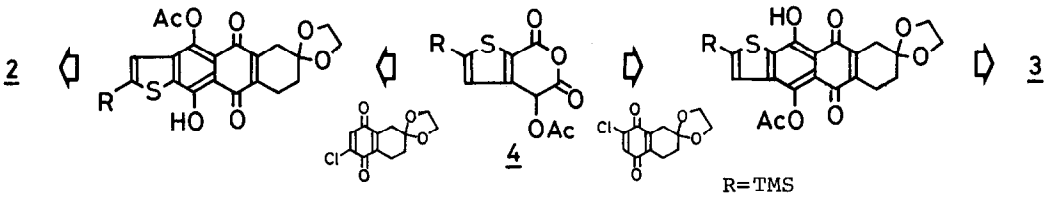
1a; R=OMe, R^1=H
b; R=OMe, R^1=OH

2

3

R=$COCF_3$

Synthetic Strategy

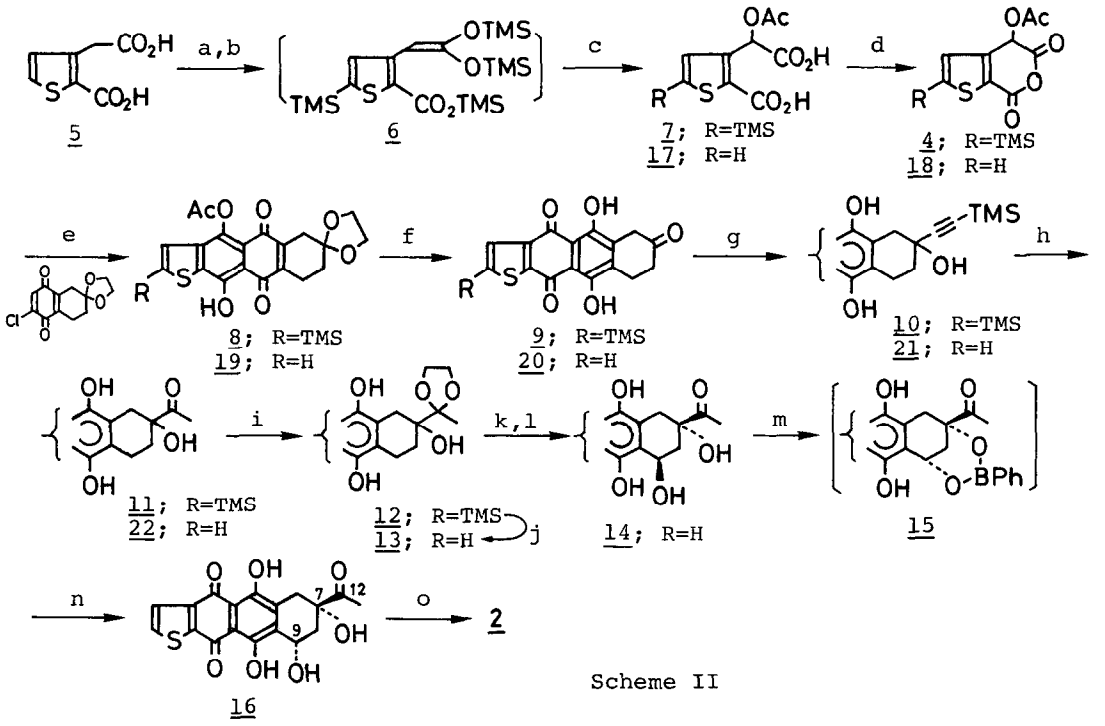


R=TMS

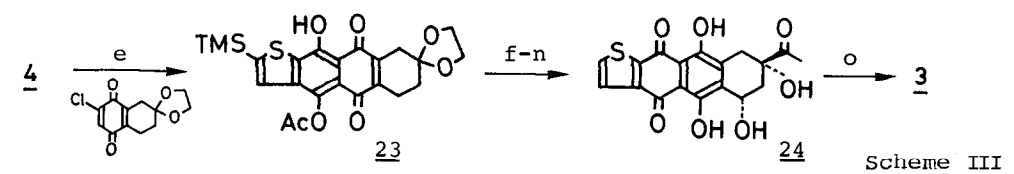
Scheme I

of trimethylsilyl chloride to give 6. Subsequent oxidation of 6 with LTA yielded 2-acetoxy-2-(2-carboxy-5-trimethylsilylthiophen-3-yl)acetic acid (7, mp 180-188°C), which was dehydrated with (trimethylsilyl)ethoxyacetylene[11] to give 4. Treatment of the sodium salt generated from 4 and NaH with 2-chloro-6-oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone 1,2-ethanediyl acetal gave the regiospecific cycloadduct (8, mp 169-175°C) in 57% overall yield from 5. Acid hydrolysis of both acetoxy and acetal groups of 8 with CF_3CO_2H-H_2O led to the triketone (9, 93%, mp 228-231°C). Trimethylsilylethynylation of 9 with trimethylsilylethynylcerium(III) reagent[8b] gave 10 (quant, mp 108-110°C), which was hydrolyzed with HgO-d.H_2SO_4 to give 11 (91%, mp 197-201°C). Attempts to convert 11, its monoacetal (12, mp 198-201°C), or the desilylated acetal (13, mp 188-192°C) into the desired aglycone (16) having cis-stereochemistry of the 7- and 9-hydroxy functions by the standard procedure[12] gave unexpected trans-diols as major products. Successful epimerization was accomplished when the desilylated trans-diol (14, mp 171-176°C) readily prepared from 13, was treated with benzeneboronic acid in the presence of CF_3CO_2H and the resulting cis-boronate (15) was deprotected with 2-methylpentane-2,4-diol-acetic acid. This gave the pure (±)-16 (86% from 14, mp 192-198°C) in 33.6% overall yield from 5. Alternatively, (±)-16 was also obtained from the desilylated acid (17) by a series of similar reactions (5→17→18→19[13]→20→21→22→13→14→15→16) in rather poor yield (12.9% overall yield from 5).

Similarly, regioisomeric (±)-aglycone (24, 20.2% overall yield from 5, mp 203-206°C) was prepared from the adduct (23, mp 188-192°C) obtained by the reaction of 4 and 3-chloro-6-oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone 1,2-ethanediyl acetal as depicted in Scheme III.



Scheme II



Scheme III

a) 4.6eq LDA/THF, b) 10eq TMSCl,-78°,1.5h, c) 1.1eq $Pb(OAc)_4/C_6H_6$,r.t.,1h; 99% from 5, d) 1.3eq TMS-≡-OEt/CH_2Cl_2,r.t.,3h; quant, e) NaH/THF,r.t.,17h, f) CF_3CO_2H-H_2O,50°,3h, g) 20eq TMS-≡-$CeCl_2$/THF,-78°,2h, h) HgO-d.H_2SO_4/THF,70°,1.5h, i) $HO(CH_2)_2OH$-p-TsOH/C_6H_6, reflux,3h; 98%, j) n-Bu_4NF/THF,r.t.,20min, k) Br_2-AIBN-H_2O/$CHCl_3$-CCl_4,70°,2h, l) CF_3CO_2H-H_2O,0°,1.5h, m) $PhB(OH)_2$-CF_3CO_2H/toluene,0°,3h→r.t.,13h, n) 2-methylpentane-2,4-diol-AcOH/CH_2Cl_2-acetone,r.t.,2h, o) i) 4-O-p-nitrobenzoyl-N-trifluoroacetyl-L-daunosaminyl chloride-$Hg(CN)_2$-$HgBr_2$,MS 3A/$CHCl_3$,r.t.,30min, ii) prep.TLC, iii) 0.1N NaOH/CH_2Cl_2-MeOH,0°,30min

With each aglycone in hand, there remained the glycosidation with appropriately protected L-daunosamine as the target. Thus, the employment of the recently developed useful method[14] for the glycosidation of aglycones (16 and 24) gave the α-glycosides (2 and 3) in rather poor yields. The employment of the classical Koenigs-Knorr method for the glycosidation of 16 and 24 with 4-O-p-nitrobenzoyl-N-trifluoroacetyl-L-daunosaminyl chloride[15] gave better yield of the mixtures of α- and β-glycosides. Separation of the mixture by preparative TLC followed by alkaline hydrolysis gave the pure α-glycosides, 2 [28%; mp 145-150°C; $[\theta]_{295}^{max}=-1.15\times10^4$ (EtOH); $[\alpha]_D^{25}+152°$ ($CHCl_3$, c 0.05); mass spectrum (FAB), m/z 598 $(M-H)^-$], and 3 [30%; mp 147-155°; $[\theta]_{295}^{max}=-3.97\times10^4$ (EtOH); $[\alpha]_D^{25}+34°$ ($CHCl_3$, c 0.05); mass spectrum (FAB), m/z 598 $(M-H)^-$], respectively. The stereochemistry of the glycoside linkage could be determined from their 500 MHz ^{1}H-NMR and CD spectral data. All of the products gave

satisfactory analytical data.

It is worth noting that the present D-ring thiophene analogs (2 and 3) show inhibition activity against L-1210 cell growth (in vitro) comparable to 1a,b. The preparation of other D-ring heteroanthracyclines by the use of this synthesis and biological testing are in progress.[16]

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